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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,635	11/25/1997	ELIZAR RABBANI	ENZ-5&DIV3	9132

ENZO THERAPEUTICS
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EXAMINER

SCHMIDT, MARY M

ART UNIT	PAPER

DATE MAILED: 04/21/2000

33

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
08/978,635	RABBANI ET AL.
Examiner	**Art Unit**
Mary M. Schmidt	1635

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *245-251* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *245-251* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 1997* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1☐ Certified copies of the priority documents have been received.

2☐ Certified copies of the priority documents have been received in Application No. _____.

3☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *32*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Drawings

1. The drawings are objected to as set forth in the PTO-948 mailed with the Office Action dated 12/06/2002.

Election/Restriction

2. Applicant's election with traverse of (1) Intron for claims 245 and 246; (2) Antisense RNA for claims 245 and 247 in Paper No. 31, filed 1/8/03, is acknowledged. The traversal is on the ground(s) that "Although 35 U.S.C. 121 provides that restriction may be required to one or two or more independent and distinct inventions, 37 C.F.R. 1.141 provides that a reasonable number of species may still be claimed in one application if the other conditions of the rule are met. Applicants note that in group (1), there are only four species recited, in groups (2), there are only seven species recited. It would certainly not be unduly burdensome to search such a small and limited number of species. Furthermore, the species in each of the specified groups are related to each other. Specifically, the claims in (1) are directed to RNA processing elements and the claims in group (2) are directed to the nucleic acid product. Applicants respectfully request, therefore, that the rejection be withdrawn." This is not found persuasive because although applicant asserts that the number of species is relatively small and that the species are all related, the combination of all the different species as claimed has not been taken into account by applicant. Furthermore, the species are so broad in themselves (ie. for example, the species

Intron and Antisense RNA) that the search burden for each is not specific and distinct since each species would require a broad search due to the quantity of literature associated with each species.

The requirement is still deemed proper and is therefore made FINAL. However, due to the high level of structural and functional similarity between a ribozyme and an RNA antisense (the elected species of claim 247), the species ribozyme is now considered part of the elected invention for the purposes of examination below since a ribozyme as part of itsfunction binds as an antisense RNA to a target complementary sequence.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 245-251 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 245 is drawn to a process for selectively expressing a nucleic acid product in a cell, which product requires processing for functioning, said process comprising; (I) providing a nucleic acid construct which when introduced into a cell produces a nucleic acid product

comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed from the nucleic acid product during processing of the nucleic acid product and (ii) introducing said construct into said cell. Claim 246 further limits the processing element to comprise an RNA processing element such as an intron. Claim 247 further limits the nucleic acid product to an antisense RNA and/or a ribozyme. Claim 248 specifies wherein the construct is introduced *ex vivo* in to said cell. Claim 249 specifies wherein said construct is introduced *in vivo* into said cell. Claim 250 specifies that the construct is introduced into a biological system containing said cell. Claim 251 specifies that the biological system is selected from the group consisting of an organism, an organ, a tissue, a culture, and a combination of the foregoing.

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

Furthermore, vectors ultimately designed for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data. Specifically, construction of the M13 phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make

pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "A" antisense T7 operon , the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC

(when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function

and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The claims lack written description since a representative number of species of the constructs claimed (and specifically the embodiments elected as species) for use in a cell are not adequately described by the specification as filed. The claims are drawn to methods of selectively expressing a nucleic acid product, such as an antisense RNA, in a cell from a set of constructs comprising a non-native processing element, such as an intron, which when in a compatible cell is substantially removed from the nucleic acid product during processing of the nucleic acid product. As summarized above, the written description requirement requires that a "art-recognized correlation or relationship between he structure of the invention and its function" is known at the time the invention was made. Further, one of skill in the art must be able to "immediately envisage the product claimed from the disclosed process..." Although, the specification as filed has shown (in the figures especially), numerous vector-like constructs, the only species of an intron containing construct for expression of an antisense is that of the U1 cassette construct with antisense to HIV expressed therefrom in a cell in cell culture. One of skill in the art would not have recognized that applicant was in possession a representative number of other species of the broad genus of constructs claimed having other intron segments which are processed away from the antisense, nor having other antisense with a known antisense function. In regards to the breath of antisense claimed, design of an antisense is based on knowledge of the target gene nucleic acid structure. One of ordinary skill in the art would not have recognized that

applicant was in possession of a representative number of species of antisense (or ribozyme) to any target gene from the teachings of the specification as filed. Thus, absent further specific (not general) guidance for the nucleic acid structure of other introns useful as non-native processing elements (note that the information is also needed as to which cells, or cell types (tissues), are compatible with the particular intron used), as well as specific guidance for antisense to other target genes (or the specific target use sequence from which to design the antisense) would have been necessary for one of skill in the art to immediately envisage other representative species of the claimed genus of constructs useful in the claimed cells. Furthermore, neither the specification nor the prior art taught a representative number of species of the claimed constructs having the function of use in cells in a whole organism, via administration either *in vivo* or *ex vivo*. The examples in the instant specification as filed do not teach the direct correlation between any such vector constructs (including the U1-anti-HIV constructs) as having a specific function in a cell in a whole organism.

5. Claims 245-251 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (*in vitro*), does not reasonably provide enablement for methods of expressing the nucleic acids in a whole organism (*in vivo*). The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

Claim 245 is drawn to a process for selectively expressing a nucleic acid product in a cell, which product requires processing for functioning, said process comprising: (I) providing a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed from the nucleic acid product during processing of the nucleic acid product and (ii) introducing said construct into said cell. Claim 246 further limits the processing element to comprise an RNA processing element such as an intron. Claim 247 further limits the nucleic acid product to an antisense RNA and/or a ribozyme. Claim 248 specifies wherein the construct is introduced *ex vivo* in to said cell. Claim 249 specifies wherein said construct is introduced *in vivo* into said cell. Claim 250 specifies that the construct is introduced into a biological system containing said cell. Claim 251 specifies that the biological system is selected from the group consisting of an organism, an organ, a tissue, a culture, and a combination of the foregoing.

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A

second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

Furthermore, vectors ultimately designed for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data. Specifically, construction of the M13 phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

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DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Thus, for the elected claimed invention, expression of antisense and/or ribozymes from vectors having a non-native processing element, in a cell, no such antisense or ribozyme constructs were taught in the specification as filed as reduced to practice for expression of the claimed constructs in cells in a whole organism.

There is a high level of unpredictability known in the antisense and relative ribozyme art for *in vivo* (whole organism) applications. The following references primarily refer to the unpredictability of administration of antisense oligonucleotides, but may also be applied to antisense expressed from a vector since the function of the antisense is the same, to locate and bind a target gene, thereby decreasing its expression. The factors considered barriers to

successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." When expressed from a vector, the antisense must retain the ability to be localized to the target area. Thus use of U1 introns in the examples in the specification as filed are helpful for targeting the antisense expressed to the nucleus of the cell, but the unpredictability remains for factors such as expression levels of the antisense, the localization of the vector to desired tissues, and expression of the antisense for the recited function, inhibition of the target gene. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page

315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett

et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecule constructs *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule constructs *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Claims 248 and 249 (and 245 from which they depend) are furhter rejected for the limitation of introducing *ex vivo* and *in vivo* the construct to "a cell." Neither *in vivo*

administration nor ex vivo administration is considered administration to a single "cell", but rather to more than one cell ("cells") or tissues in the case of *in vivo*, and where multiple transformed cells are delivered to a whole organism in the case of *ex vivo*. It would be thus highly unpredictable in the art for delivery of the claimed constructs to a single cell *in vivo*, or delivery of a single transformed cell *ex vivo* to the whole organism. One of skill in the art would have to practice trial and error experimentation to introduce the construct to a single cell in a whole organism. Neither the specification nor the prior art taught methods of introducing a vector construct by injection or other routes of administration to a single cell in a whole organism. Therefore, the claims as written for *in vivo* and *ex vivo* administration to a cell are not enabled since one of skill in the art would not be able to practice the claimed methods for such administration to a single cell and the *de novo* determiniation of how to transfer to a single cell *in vivo* or *ex vivo* would be considered an undue amount of experimentation absent further guidance in the specification as filed.

Response to Arguments

6. Applicant's arguments filed 07/17/2002 have been fully considered but they are not persuasive.

Applicant's state that "it would not require undue experimentation for the ordinary skilled artisan to practice the invention. A sufficiently detailed description is provided in the specification for practicing the method of the present invention. Specifically, on page 83, lines 5-

7, a "processing element" is defined as "an RNA processing element including but not limited to an intron, a polyadenylation signal and a capping element, or combinations of the foregoing". A compatible cell is described on pages 87-90. A specific example is described on page 89, where an intron is introduced into the coding sequence of T7 RNA polymerase.... Furthermore, a description of the method of the present invention is provided on page 83, line 13 to the bottom of page 84.... A specific embodiment of the present invention is described on page 146-152."

Note that these examples provided in the specification as filed are drawn toward construction and use of the above described U1-antisense vectors in cells in cell culture, and the instant rejection has been modified to a scope of enablement rejection, where the *in vitro* use of the claimed vectors is enabled.

In regards to the Branch and Flanagan references previously cited and reiterated above, applicant argues that they "were actually published after the priority date of the above-referenced application. The MPEP 2164.05(a) states that "the state of the prior art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." This section further states "In general, the examiner should not use post-filing date reference to demonstrate that the patent is no-enabling.""

In response, the Branch, Flanagan and other newly cited references above are relied upon to teach that even today, there is a high level of unpredictability in the art for design and use of antisense in whole organisms due to the complexity of the whole organism environment and the number of unpredictable factors argued above.

Applicants further "assert that there are a number of publications available as of the priority date of the above-referenced application which express a more optimistic attitude regarding the suitability of antisense to become useful in therapeutic application. One example of such a publication is Crooke, 1994, Antisense Research and Development 4:145-6, attached hereto as Exhibit 1. Another example is Liu et al., 1997, J. Virol. 71:4079-4085, attached hereto as Exhibit 2 which discloses Tat-activated expression of chloramphenicol acetyltransferase was shown to be specifically inhibited in cells expressing Tat and transactivation response region antisense sequences."

In response, the Liu et al. article is a publication of the constructs and experiments taught in the instant specification. However, the Liu et al. paper does not further provide any *in vivo* context of use for the disclosed constructs. While they state on page 4085 that "[t]he choice of U1 as an antisense carrier provided structural stability and nuclear localization", they further state that "[t]his successful approach in cell culture is being developed as means of achieving a high level of stable resistance in patent cells for the purpose of developing an ex vivo therapy for treating HIV infections." Thus, the *in vivo* uses are "being developed" and were not show at the time the invention was made to function *in vivo*. The Crook reference does not further provide an specific expectation of success for the instantly disclosed constructs to function *in vivo* either.

Applicant further states that "It is also Applicants' position that in vivo data is not necessary. As noted in the MPEP Section 2107.03, III, "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition

had been established prior to the filing of the application." However, Applicants note that clinical trials were underway by the assignee of the instant application around the priority date of the above-referenced application. A press release dated July 10, 1996 is attached hereto as Exhibit 3. The results to date have generally been favorable and are publicly available."

The above rejection does not imply that an animal model of a disease is needed to enable the instantly claimed invention. The rejection is centered on the ability to a make and use the claimed methods with any expression construct as claimed, and the position has been maintained, based on the references cited, that there is a high level of unpredictability in the art of design and use of antisense in a whole organism. Although applicants state that clinical trials are underway, the information in Exhibit 3 does not teach what constructs are in trials and whether or not they function as instantly claimed in the context of a whole organism.

7. Claims 248 and 249 are considered free of the prior art since the prior art did not teach nor fairly suggest the claimed methods of *in vivo* and *ex vivo* administration of the claimed constructs to a single cell.

Claims 245-251 are considered free of the prior art since the closest prior art cited in previous Official actions was DeYoung et al. DeYoung et al. is no longer considered prior art since they do not teach all the elements of claim 245. The flanking U1 sequences are not

removed from the ribozyme sequence upon administration of the plasmid to the cells and expression of the ribozyme.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader* may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

[illegible]AGER
[illegible]MINER
[illegible]30

M. M. Schmidt
March 24, 2003